

EDITORIAL COMMENT

Sympatholysis and Cardiac Sympathetic Nerve Function in the Treatment of Congestive Heart Failure*

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Activation of the sympathetic nervous system, manifested by an increase in plasma norepinephrine (NE), is a salient feature in congestive heart failure (HF). This was first thought to be an important adaptive mechanism to support the failing myocardium (1). However, evidence now indicates that activation of the sympathetic nervous system is detrimental and maladaptive. Long-term exposure of the heart to NE can cause not only myocardial β -adrenoceptor down-regulation but also cardiac hypertrophy, ischemia, cardiac arrhythmia, tissue necrosis, and myocyte apoptosis, all of which have been shown in patients with congestive HF (2). This concept is further supported by several large clinical trials showing that long-term β -blocker therapy can not only improve left ventricular (LV) systolic function but also increase survival in patients with chronic HF secondary to LV systolic dysfunction (3–5).

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Given the overwhelming success of the β -adrenoceptor blocker therapy, several investigators have looked into the possibility that more effective therapy can be derived by silencing the sympathetic nervous system activity with sympatholytic agents such as moxonidine and clonidine. Unlike clonidine, which acts on the central α -2 adrenergic receptors, moxonidine preferentially stimulates the brain stem imidazoline-1 receptor to decrease sympathetic outflow (6). Although both agents have been shown to reduce plasma NE and produce some benefits in patients with HF (7–9), the long-term Moxonidine Congestive Heart Failure (MOXCON) trial was terminated prematurely because of increased mortality in the moxonidine group (10). Similarly, a subgroup analysis of the Beta Blocker Evaluation of Survival Trial (BEST) showed that those subjects who died during the study had higher plasma NE concentration at baseline and greater reductions of plasma NE after three months of bucindolol treatment than subjects who survived (11). It was speculated that bucindolol has an effect on the

central nervous system that suppresses the sympathetic outflow (11). The authors conclude that sympatholytic agents should be given with caution to patients with severely compromised hemodynamics in whom a critical minimal adrenergic tone is important. The findings suggest that the sympathetic nervous system activation can be both adaptive and maladaptive, depending on the degree of basal sympathetic activation and the extent of sympatholysis.

In this issue of the *Journal*, Igawa et al. (12) report a study in which three doses of guanethidine were used to produce dose-dependent decreases of plasma NE in rats with HF after myocardial infarction. Guanethidine was started two days before coronary occlusion and continued for 28 days after myocardial infarction. All three doses of guanethidine improved the short-term survival after coronary artery occlusion, but only the low-dose guanethidine (1 mg/kg/day) reduced LV dilation and improved LV mechanical function and survival over 28 days. When the high dose of guanethidine (10 mg/kg/day) was administered, only three of 34 rats survived four weeks. An intermediate dose of guanethidine produced no beneficial effects on either cardiac hemodynamics or four-week mortality compared with the control group. Results of the study indicate that the effects of sympatholytic agents are dose-dependent and that excessive sympathetic inhibition may be deleterious in HF.

However, unlike bucindolol in the BEST study, long-term use of carvedilol reduced cardiovascular mortality and morbidity in patients with very severe HF in whom removal of the noradrenergic drive by β -receptor blockade was expected to exert a negative effect (13). Thus fundamental differences may exist between sympatholysis and β -receptor blockade in their delivery of an anti-adrenergic effect. Furthermore, unlike moxonidine and bucindolol, guanethidine acts on the peripheral sympathetic nerves to reduce NE release. Ultrastructural and immunohistologic changes such as those produced by immune-mediated neuronal degeneration have been shown to occur in the peripheral sympathetic nerves after guanethidine treatment (14,15). This raises a question whether the harmful effects of guanethidine reported in the study by Igawa et al. (12) were related to destruction of the cardiac sympathetic nerves.

Recently, radio-iodinated metaiodobenzylguanidine (^{123}I -MIBG), a structural analogue of NE, has been used to study the integrity and function of the cardiac sympathetic nervous system (16). The failing heart is characterized by reduced washout and distribution of MIBG on myocardial scintigraphy. Studies have shown that cardiac sympathetic nerve innervation as demonstrated by MIBG scintigraphy is an independent predictor for fatal outcomes in patients with HF (17). More importantly, the beneficial effects of carvedilol (18), metoprolol (19), spironolactone (20), and enalapril (21) are associated with improvements in cardiac sympathetic innervation. In contrast, bucindolol therapy, which showed only marginal survival benefits (22), did not im-

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prove the sympathetic nerve function as measured by MIBG (23).

Our laboratories have studied the pre- and post-synaptic changes of the cardiac sympathetic nerve function in experimental HF. We were the first to demonstrate a chamber-specific reduction of myocardial β -receptors, occurring only in the failing right ventricle of dogs with right-heart failure produced by tricuspid avulsion and progressive pulmonary artery constriction (24). The decrease of myocardial β -adrenoceptor density is linked to reduced NE uptake activity, NE uptake-1 carrier density (25,26), and increased interstitial NE (27). Furthermore, because myocardial NE uptake is also reduced by exogenous NE administration, we speculate that the changes of the sympathetic nerve terminal function in HF are caused by the increased interstitial NE concentration (27). The functional importance of the NE uptake site was further studied in rabbits at various time intervals after the start of rapid ventricular pacing (28). We found that rapid ventricular pacing caused early sympathetic nervous system activation, followed in sequence by reduced myocardial NE uptake, loss of neuronal NE, and down-regulation of myocardial β -adrenoceptors. In addition, long-term use exogenous NE has been shown to reduce myocardial NE uptake and β -adrenoceptor receptor density in normal animals without HF (29). The interdependence of increased sympathetic stimulation, decreased cardiac NE uptake, and myocardial β -adrenoceptor down-regulation is further borne out by a recent study by Leineweber et al. (30), who found that neurohumoral activation is essential for the reduction of myocardial β -receptors in the hypertrophied right ventricle produced by monocrotaline, which, similar to our earlier studies in right-heart failure (24,25), is characterized by a chamber-specific reduction of myocardial NE uptake sites (31).

The functional importance of the NE reuptake mechanism in the regulation of myocardial β -receptor density and post-synaptic β -adrenergic inotropic responsiveness was further studied in the right-heart-failure animals treated with desipramine (32). Unlike guanethidine, desipramine blocks neuronal uptake of NE at the sympathetic nerve terminals without destroying sympathetic nerves. We found that desipramine facilitated the reduction of myocardial β -adrenoceptor density and β -adrenergic subsensitivity in the animals. In contrast, selegiline, which is a central α_2 -agonist with a neuroprotective effect, attenuated the increase in plasma NE and the decrease of myocardial β -receptor density and improved cardiac mechanical function in pacing-induced cardiomyopathy (33). Selegiline also prevented the reductions of NE uptake activity, NE uptake-1 carrier site density, and sympathetic neurotransmitter profiles in the failing heart.

Our studies suggest a revised paradigm for the treatment of congestive HF. While interventions should be directed toward minimizing the noradrenergic release of NE or blocking the harmful apoptotic and oxidative effects of NE on the sympathetic nerves and cardiomyocytes in HF,

attention should be paid to preserving the integrity and NE reuptake function of the sympathetic nerve terminals. Guanethidine produces marked inhibition of the sympathetic nerve activity and plasma NE, but at high doses it also exerts a negative effect on the functional integrity of the sympathetic nerve terminals. Cardiac interstitial NE may have increased further and contributed to the clinical adverse effects of guanethidine (12). Whether moxonidine affects NE uptake or storage in the sympathetic nerve terminals is not known. In addition to selegiline, guanabenz—also an α_2 -agonist—has been shown to improve cardiac sympathetic NE and tyrosine hydroxylase activity in animals with aortic constriction (34). At least three different presynaptic α_2 receptors have been identified and shown to control NE release in HF at present. Brede et al. (35) reported recently that progression of HF produced by aortic constriction was worsened in gene-targeted mice lacking either an α_{2A} or an α_{2C} receptor subtype but not in mice lacking the α_{2B} receptor subtype. It is clear that much remains to be learned about how the α_2 receptor-mediated events affect the progression of HF and about whether novel sympatholytic agents can be developed to reduce the noradrenergic drive while preserving the integrity of the sympathetic nerve terminal function.

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